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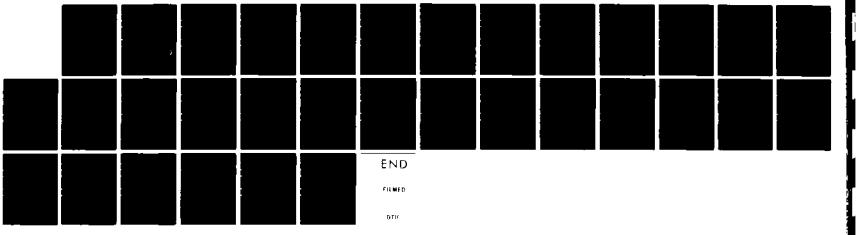

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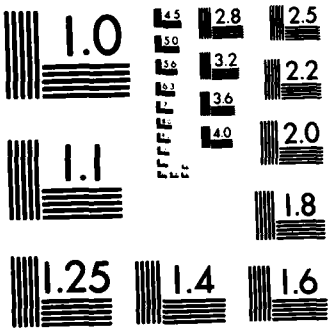

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Investigation of Vision and Performance after Administration of Cholinergic Blocking Agents

III. Atropine

Final Report

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This report covers two visual performance experiments conducted in 1982 as part of our investigation of the effects of atropine on human performance. The first experiment evaluated five dose levels of atropine (zero to 2 mg/70 kg bodyweight) on a military performance task. We worked in conjunction with the Ocular Hazards research team at Letterman Army Medical

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20. Abstract (continued)
Center to conduct this experiment using their BLASER tank tracking simulator. We also investigated the effects of atropine dose levels on several persistent ocular side effects, and we attempted to more thoroughly assess the subjective symptoms experienced by our subjects.

In the second experiment we studied the effect of three dose levels of atropine (0, 1, and 2 mg/70 kg bodyweight) on the ability of subjects to perform two simultaneous and asynchronous performance tasks. Subjects sat in a Barany chair moving sinusoidally at 0.5 Hz while performing a visual-motor tracking task and a tone discrimination task. The complexity of the combined tasks was meant to simulate, in a controlled manner, tasks performed in military environments. This experiment was designed in order to evaluate the effects of atropine on men in stressful situations.

In the first experiment we found that atropine had no significant effect on the simple tank tracking task for doses of 0.25-2mg/70 kg bodyweight. We measured prolonged but functionally unimportank ocular side effects that persisted for at least 44 hours after administration of the 2 mg dose in some subjects. Subjectively, subjects were able to notice atropine effects for doses as low as 0.5 mg, and at the higher doses the most pronounced effects were a dry mouth and increased fatigue. In the second experiment we found that atropine reduced pursuit tracking performance levels by small but statistically significant amounts for the most difficult visual tracking stimuli with the 2 mg dose. In summary, we find that doses of 1 mg or less do not significantly interfere with performance levels in simple or complex tasks and that 2 mg appears to be a threshold for reduction in performance levels. The persistent ocular effects caused by the 2 mg dose level of atropine are not large enough to degrade visual performance in young men.

FOREWORD

This is the Final Report for a study supported by the U.S. Army Research and Development Command (Contract No. DAMD 17-80-C-1216) awarded to the Visual Sciences Division of Optical Sciences Group, Inc., of Petaluma, California. A major portion of the study was conducted at the Smith Kettlewell Institute of Visual Sciences at the Pacific Medical Center in San Francisco and we gratefully acknowledge the space, facilities, and services provided by the Institute. In particular, we would like to acknowledge the essential secretarial and administrative services provided by Catherine Carver. We would also like to thank Marc Cruciger, M.D., Elbert Magoon, M.D., Nieca Caltrider, M.D. and Eric Whikehart, M.D. for providing medical services during the experiments.

We are very pleased to be able to acknowledge the superb cooperation which we received from Colonel Edwin Beatrice and his staff at Letterman Army Institute of Research. Although singling out a single individual for special thanks brings with it the risk of offending others, we must thank David Stamper for his assistance in design of the Blaser experiment, for his patience with our experimenters and subjects and for providing a draft manuscript describing the Blaser experiment and results which has been incorporated into this report.

As always we must thank our anonymous subjects whose patience and good humor made the conduct of these experiments a much less arduous task.

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

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INTRODUCTION

Atropine sulfate, which is administered in an autoinjector, is currently the drug of choice as an antidote to nerve gas poisoning of troops in the field. Each injector contains a 2 mg dose and it is recommended that no more than three doses be administered at any one time. As with many drugs, atropine can produce undesirable side effects on general physiological and visual functions which could affect the performance of troops in a combat situation (e.g., Baker et al., 1982). These studies do not address the more general questions of performance in military situations, however. Information regarding the effects of atropine on performance is needed.

There is almost universal agreement in the literature that atropine in doses above 4 mg produces effects on pupil size and near vision function. Cullumbine, McKee and Creasey (1955) found that all 44 of their subjects complained of blurred vision after 5 mg of atropine, but only 3 of the 44 reported blurred vision after 3 mg. The pupils were fully dilated by all doses used, and there was no change in Snellen distance acuity or in the light or accommodation pupillary reflexes. Some complaints of difficulty in reading were reported after repeated doses of 2 mg of atropine on 5 successive days. Mirakhur (1978) reported data on the time course of atropine action, noting that effects of 2 mg on pupil size and near point of accommodation persisted beyond 6 hours.

Moylan-Jones (1969) found that atropine in doses up to 6 mg impaired alertness, efficiency and energy, produced disorders of perception in 10 of 23 subjects, impaired performance on a number facility task, map and compass reading task and also impaired performance on a digging task. Subjective effects lasted up to 21 hours after drug administration, and pupil dilation was an almost universal finding. No mention was made of problems with near vision, which is surprising in view of the data reviewed by Headley (1982); of the four studies he reviewed where doses up to 5 mg of atropine were administered, all of the subjects reported blurred near vision at doses of 4 and 5 mg. Further confirmation of the effects of larger doses of atropine was provided by Rozsival and Ciganek (1978) who reported substantial reduction in acuity at near after 4 mg of atropine. Headley emphasized the paucity of data on the higher doses of atropine on visual function and notes that "time-course studies which can document the onset, duration, and time to maximal effect are lacking."

Studies of the effects of atropine on memory and cognitive variables are scattered and incomplete, especially as they relate to tasks of direct

military relevance. Wetherell (1980) reports that atropine in 2 mg doses produces decrements in short-term memory performance as assessed by a digit recall test and an associative memory test. Holland, Kemp and Wetherell (1978) reported similar findings for effects of 2 mg of atropine on "number facility," as well as for reaction time and pursuit motor performance. Our data show small performance decrements with 2 mg of atropine on visual search (Baker et al, 1982) and on two different pursuit tracking tasks.

In assessing the studies of the cognitive effects of atropine, Headley acknowledges the insufficiency of knowledge of the cognitive psychopharmacology of atropine. He notes that the effects of higher doses of atropine on short-term memory, decision making, reaction time and visual search tasks require further study.

EXPERIMENT I

Current trends in anti-armor warfare include wire or laser guided artillery rounds or missiles. A key element in the success of these anti-armor weapons is the ability of the human operator to guide the projectile to the target. To successfully complete a firing mission requires a highly trained and skilled operator. Previous work has shown tracking performance with the BLASER simulator to be comparable to performance in the field using the actual weapon systems (see O'Mara et al., 1979). The BLASER simulator should provide a sensitive means of evaluating the effects of increasing doses of atropine on a military performance task.

In this first experiment, 10 subjects were given each of 5 doses of atropine (including placebo) and were tested on a pursuit tracking task using the BLASER system. The trials were run under both bright and low ambient light conditions. We were unable to show performance decrements produced by atropine at either light level for any dose of atropine, although there was some evidence of increased variability of response at the 2 mg dose of atropine.

METHODS

Ten male volunteers participated in this study. The ages of the volunteers ranged from 20-32 years with a mean of 25 years. The body weights ranged from 56-108 kg with a mean of 75 kg. Each subject was given a screening examination to determine if he was fit to participate in this project. None of the volunteers had received any prior practice with a viscous-damped tracking device. The subjects all happened to be Caucasian and, on the average, had completed 3.5 years of college. One subject had previous military experience.

The subjects received one of five atropine dose levels on each test day. The order of presentation of each dose was balanced using a Latin Square design so that each volunteer received each dose once. The five dose levels were:

1) 0.00 mg (placebo)
2) 0.25 mg
3) 0.50 mg
4) 1.00 mg
5) 2.00 mg

Doses were adjusted to body weights above and below 70 kg. Each dose was given as an intramuscular injection in the upper arm. The attending physician was the only individual aware of the dose administration schedule during the experiment.

The BLASER simulator includes a laboratory constructed viscous-damped, designator tracking device which is mounted in a sandbag bunker. The tracking device opens onto a scale model terrain area through a porthole in the front of the bunker. Scale model tanks, with an infra-red light emitting diode (LED) mounted on the side, move in a fixed arc at a simulated distance of 1 km and a constant angular velocity of 5 milliradians/second. The tank scene is imaged by a television camera which is mounted coaxially with the optics of the designator, with the LED signal providing a reference point to electronically monitor tracking performance. Reduced ambient lighting conditions were simulated by inserting a 3.6 N.D. filter in the optical pathway. The average terrain luminance without the filter was 340 cd/m^2 and with the filter .085 cd/m^2. Separate horizontal and vertical axis tracking scores were computed for each trial based on the standard deviation of the mean absolute angular tracking error expressed in micro-radians. These tracking scores were averaged over ten trials for each session.

Each volunteer was shown the BLASER area, and the nature of the tracking task was explained to him. Each participant then began two days of practice following a massed/distributed practice schedule. During each session of the first day the massed practice entailed 11 one-minute tank-tracking trials under high ambient light conditions and another 11 trials under dim ambient light conditions. There was approximately one minute between trials and a 10 minute low-light adaptation period preceding the 11 dim light trials; during this time the subject sat in the darkened bunker. After each tracking episode, summary information was given to the subject, in the form of a percent time-on-target score and a horizontal error score

to provide performance feedback. During the second session of that day the presentation order of the bright and dim lighting conditions was reversed.

On the second day three distributed practice sessions consisting of sixteen 15 second trials under bright light and sixteen under dim light conditions were given. Again, the approximate time between trials was 1 minute, a ten minute low-light adjustment period preceded the dim light trials, and the order of the dim/bright light trials was alternated.

Following the two training days was the first of five drug test days. On each day, three tracking sessions were given, and each session consisted of ten trials conducted under bright light and ten trials under dim light conditions. The order of the bright/dim trials during the first experimental session across the ten participants was randomized in an exhaustive sequence so that five subjects began under bright light conditions and five began under dim light conditions. For each subsequent session the bright/dim presentation order was alternated based on each subject's previous session.

Following the first session of each experimental day and 30 minutes before the second session the atropine (or placebo) was given by intramuscular injection. The second tracking session was then started 30 minutes after the injection, and was followed by a one hour rest period. The third session for the day was begun 90 minutes after the injection.

The study was planned as a 2 (light level) x 2 (post-injection time) x 5 (dose level) multifactorial design with all factors treated as repeated measures. Separate analyses of variance (ANOVA) were computed for horizontal and vertical tracking scores using Biomedical Computer Programs BMC-P2V for multifactorial mixed designs. The post-injection scores for each subject were subtracted from the corresponding baseline pre-drug scores before analysis.

In the BLASER atropine experiment several visual parameters were measured on a daily basis in order to detect any atropine related ocular changes 20 to 44 hours after drug administration. Our previous experiments have shown that there is significant pupil dilation and a 1-2 diopter loss of accommodative amplitude 4-5 hours after administration of a 2 mg per 70 kg atropine dose. Our schedule allowed 48 or 72 hours between administration of drug doses, and we assumed that any persistent ocular side effects would be functionally insignificant and that cumulative dose effects would also be very small and unlikely to affect tracking performance. (Based on our experimental results these assumptions were reasonable.)

Every weekday morning for two weeks two subjects reported to our laboratory for a series of vision measurements. The subjects were then provided lunch and performed the BLASER tank-tracking sessions during the afternoon. All pre-drug measurements were made on the right eye with the left eye patched. Distance visual acuity was measured using a printed Bailey-Lovie eye chart (Bailey and Lovie, 1976) under bright illumination (87% contrast, 68 cd/m^2). The pupil size was measured while the subject fixated on one letter of the acuity chart. A pupillometer based on a design by Saladin (1978) was used to obtain an average pupil diameter under daylight conditions approximating those of the BLASER system.

Monocular nearpoint of accommodation was measured by asking the subject to bring a card of printed matter towards the eye until the print began to blur. Three measures were averaged. We then determined the accommodative near point by a method that limited the cues to accommodation to a minimum using an optical system similar to that used in the BLASER system. The subject passively looked through the eyepiece of an optical system at an acuity chart 3 meters away while the optical system was adjusted to move the image of the acuity chart slowly towards the subject. The subject reported when the letters could no longer be kept clear enough to read. Three measures were averaged.

The remaining measurements were done after the subject had visually adapted to dimly lit conditions that simulated the dim light test conditions of the BLASER facility. We measured the accommodative level of the eye while the subject looked through an optical system similar to the one used in the BLASER apparatus. The subject viewed a small, dimly illuminated spot through the eyepiece of a variable power optical system with an initial lens power of +2 diopters. This lens power was reduced, and the subject indicated when the spot first became clear. This was measured three times and the average used to estimate the instrument induced accommodative state of the eye.

Visual acuity and pupil diameter were also measured under the dim light conditions. The acuity was determined using a series of projected S chart slides (Flom, Weymouth and Kahneman, 1963), each with a group of eight Landolt rings embedded in a five by five array of other letters. A sequence of S chart slides was shown with Landolt rings of progressively smaller size down to the equivalent of 20/13 in Snellen notation. The acuity targets had a contrast of 97% with a background level of 0.6 cd/m^2.

We recalled each of our subjects 4-6 weeks after completion of the experiment for retesting of the visual functions that were measured each

day during the experiment. We did not find any long lasting effects of atropine after this length of time.

RESULTS

The group averaged tracking scores for horizontal and vertical axes are presented in Table I. The results of an analysis of variance of the post-drug minus pre-drug session tracking scores are given in Table II. The ANOVA analysis of the horizontal and vertical tracking scores showed no significant effects for any of the three main factors (i.e., dose level, post-injection time, or light level). This result appears surprising since the tracking scores with dim ambient light are uniformly higher than those with high ambient light. However, since the data used for this analyses were post-minus-pre scores, a nonsignificant finding could be expected if there were no drug effects. A subsequent analysis performed using the raw tracking scores showed a significant difference between low and high light conditions ($ss = .42652$, $df = 1$, $F = 142.62$, $P < .001$).

TABLE I

Summary of BLASER tracking scores averaged across subjects
Dose in mg/70 kg, Time in minutes, scores in microrads, +/- one SD, N=10

Dose	Time	Horizontal Axis		Vertical Axis	
		Dim	Bright	Dim	Bright
	-30	189 +/- 39	82 +/- 27	59 +/- 20	35 +/- 11
Placebo	+30	162 +/- 39	69 +/- 10	54 +/- 12	35 +/- 16
	+90	160 +/- 44	76 +/- 12	58 +/- 13	38 +/- 21
	-30	168 +/- 29	74 +/- 20	62 +/- 10	42 +/- 18
0.25	+30	157 +/- 29	68 +/- 11	61 +/- 13	42 +/- 18
	+90	160 +/- 32	67 +/- 9	54 +/- 15	44 +/- 20
	-30	190 +/- 64	70 +/- 12	54 +/- 15	34 +/- 15
0.50	+30	163 +/- 29	65 +/- 9	55 +/- 17	33 +/- 15
	+90	159 +/- 31	68 +/- 6	51 +/- 15	34 +/- 15
	-30	182 +/- 57	74 +/- 11	65 +/- 17	39 +/- 17
1.00	+30	158 +/- 52	67 +/- 9	59 +/- 17	38 +/- 21
	+90	161 +/- 41	71 +/- 6	62 +/- 18	40 +/- 17
	-30	189 +/- 63	67 +/- 12	63 +/- 23	36 +/- 17
2.00	+30	173 +/- 50	73 +/- 14	72 +/- 38	39 +/- 17
	+90	164 +/- 43	69 +/- 15	61 +/- 16	46 +/- 35

TABLE II

Summary of ANOVA* for the post-drug minus pre-drug tank tracking scores

Source	Degrees of Freedom	Horizontal Mean Square	F	Vertical Mean Square	F
Mean	1	.00526	.80	.00006	.11
Error	8	.00661		.00056	
Dose Level	4	.00192	1.38	.00027	1.36
Error	32	.00139		.00020	
Time	1	.00073	1.14	.00046	1.26
Error	8	.00064		.00034	
Dose x Time	4	.00022	.33	.00008	.38
Error	32	.00070		.00021	
Light Level	1	.00036	.14	.00020	2.18
Error	8	.00263		.00009	
Dose x Light	4	.00041	.36	.00015	1.26
Error	32	.00115		.00012	
Time x Light	1	.00019	.71	.00009	.33
Error	8	.00027		.00026	
Dose x Time x Light	4	.00066	.75	.00038	1.73
Error	32	.00089		.00022	

* The analysis was performed using Biomedical Computer Programs BMD-P2V

The vital signs, visual, and subjective questionnaire data were averaged across subjects and standard deviations included in our tables to show the extent of intersubject variability. We determined whether any significant differences occurred by testing inter-session differences using a nonparametric statistical test. Each subject served as his own control. We subtracted post-drug from pre-drug data for each subject and removed possible diurnal effects by calculating the corresponding placebo post-drug minus pre-drug difference to get an adjusted inter-session difference. For each variable these adjusted differences were ranked by sign and magnitude, and the Walsh test was used to test for statistical significance of any set of adjusted differences for the ten subjects.

We have found in previous experiments that pulse rate elevation reliably indicates when a 2 mg dose of atropine has been administered. In this experiment we found that only the 2 mg dose produced a statistically significant pulse elevation at 75 minutes after injection (see Table III). The mean adjusted pulse increase was 8 beats/min for the 1 mg dose and 23 beats/min ($p<.005$) for the 2 mg dose. Three hours after injection the pulse had returned to pre-drug levels in 7 out of 10 subjects given the 2 mg dose.

TABLE III

Summary of the vital signs data averaged across subjects
Dose in mg/70 kg, Time in minutes, BP's in mm Hg, +/- one SD, N=10

Dose	Time	Pulse	Systolic BP	Diastolic BP
	-45	71 +/- 11	113 +/- 15	73 +/- 8
Placebo	+75	71 +/- 11	111 +/- 16	76 +/- 12
	+195	71 +/- 9	110 +/- 14	75 +/- 11
	-45	70 +/- 8	112 +/- 15	75 +/- 7
0.25	+75	68 +/- 13	110 +/- 19	74 +/- 11
	+195	68 +/- 12	111 +/- 14	76 +/- 9
	-45	72 +/- 10	109 +/- 9	73 +/- 7
0.50	+75	69 +/- 9	106 +/- 10	70 +/- 6
	+195	69 +/- 12	108 +/- 8	73 +/- 6
	-45	74 +/- 9	113 +/- 14	72 +/- 9
1.00	+75	82 +/- 8	111 +/- 17	79 +/- 12
	+195	72 +/- 10	111 +/- 16	79 +/- 10
	-45	73 +/- 10	113 +/- 14	72 +/- 9
2.00	+75	96 +/- 10	108 +/- 9	74 +/- 12
	+195	77 +/- 12	110 +/- 13	79 +/- 13

As in previous experiments blood pressure was not significantly affected by atropine in doses up to 2 mg. We might expect to see some partial compensation for the increased pulse by means of a reduction in systolic pressure or an increase in diastolic pressure or a combination of the two effects. We found that systolic pressure did not change significantly for any atropine dose. Diastolic pressure was slightly elevated at the 1 and 2 mg dose levels at 75 minutes and 195 minutes after the injection (see Table III). For the 1 mg dose diastolic pressure increased in 9 of the 10 subjects at +75 minutes yielding +3.5 mm as the only statistically significant pressure increase ($p<.056$).

Following each tracking session each subject filled out a subjective symptoms questionnaire (see appendix) which listed 19 items to be ranked on a scale of zero to four. The subject's responses were analyzed by averaging across subjects and by examining post-drug minus pre-drug differences. Only a few of the items elicited enough change to show statistically significant session and dose level differences. The items getting the greatest response are described below.

A dry mouth caused by a reduction in salivary gland activity was the symptom most commonly reported by our subjects after they received doses of 0.5 mg or more of atropine. Eight out of ten subjects reported a dry mouth 75 minutes after getting the 0.5 mg dose and the adjusted difference in ratings was 0.7 ($p<.025$). For the 1 and 2 mg doses the subjective ratings were roughly doubled and tripled respectively (see Table IV). Subjects reported that the dry mouth sensation persisted for approximately 4-6 hours after injection. All subjects were free to drink water when they were not performing the tracking task.

The ability of atropine to suppress sweat gland activity can lead to the sensation of dry skin, elevated skin temperature and erythemia. In an air conditioned environment such as the testing bunker we used, dry skin would be hard for most subjects to notice. However, in a hot environment, the inability to cool the body by the evaporation of sweat would cause dry skin symptoms to be noticed and in extreme cases lead to heat prostration. In our experiment 8 out of 10 subjects reported no dry skin symptoms (see Table IV). The first two subjects did show a pronounced and apparently dose-related dry skin and dry mouth response for the 0.5, 1, and 2 mg doses. However, the two other subjects who reported a strong dry mouth effect reported no dry skin effect at all.

TABLE IV

Summary of group averaged subjective questionnaire results
Dose in mg/ 70 kg, Time in minutes, Rating scale 0-4, +/- one SD, N=10

Dose	Time	Dry mouth	Dry skin	Intoxication
	-45	0.1 +/- .3	0.1 +/- .3	0.0
Placebo	+75	0.4 +/- .7	0.1 +/- .3	0.4 +/- .7
	+195	0.2 +/- .4	0.1 +/- .3	0.0
	-45	0.2 +/- .4	0.3 +/- .7	0.0
0.25	+75	0.4 +/- .7	0.3 +/- .7	0.1 +/- .3
	+195	0.2 +/- .4	0.3 +/- .7	0.0
	-45	0.1 +/- .3	0.1 +/- .3	0.0
0.50	+75	1.0 +/- .7	0.4 +/- .7	0.1 +/- .3
	+195	0.9 +/- .6	0.3 +/- .5	0.1 +/- .3
	-45	0.2 +/- .4	0.3 +/- .7	0.0
1.00	+75	1.7 +/- .7	0.7 +/- .9	0.4 +/- .7
	+195	1.4 +/- .5	0.4 +/- .7	0.2 +/- .4
	-45	0.1 +/- .3	0.3 +/- .7	0.0
2.00	+75	2.7 +/- .8	1.0 +/-1.5	1.0 +/- .8
	+195	2.0 +/- .9	0.5 +/- .8	0.5 +/- .7

Higher doses of atropine can produce a state of intoxication similar to that produced by other commonly used intoxicants. Our subjects reported only a few symptoms of intoxication with the 2 mg dose such as difficulty completing thoughts or a feeling of being "spaced out". Eight out of ten subjects reported being at least "a little" intoxicated on 2 mg after 75 minutes. Only one subject reported "quite a bit" of intoxication on the largest dose. Two subjects reported no intoxication for any dose and three subjects showed a mild placebo intoxication effect. Subjects commented that their intoxication was not euphoric in nature and did not impair their tracking task performance.

Self-ratings of balance and coordination attempted to elicit symptoms that might interfere with the tank-tracking task as well as such normal tasks as walking. We have found that atropine at the 2 mg dose level

causes some subjects to feel an insecurity regarding their balance while walking. Atropine, like other anti-cholinergic drugs, may have an anti-motion-sickness effect in some situations. Balance was rated as altered "a little" by 6 out of 10 subjects 75 minutes after injection of the 2 mg dose and at 195 minutes only one subject still reported an altered sense of balance. Only four of our ten subjects noted a slight alteration of coordination at the high dose of 2 mg 75 minutes after the injection and this was not statistically significant.

Fatigue can be attributed to physical exhaustion, boredom or drowsiness. The slight sedative effect of atropine usually causes some drowsiness and "fatigue" was the closest symptom listed on our questionnaire. The placebo produced more fatigue symptoms than all but the 2 mg atropine dose. Even though it was not statistically significant the 2 mg dose produced "quite a bit" of fatigue in 3 out of 10 subjects 75 minutes after injection. Subject #8 reported that "I was dozing off between runs during the last group of ten (tracking episodes)" yet his averaged tracking scores did not reflect a performance decrement. Two subjects noted no fatigue effects for any atropine dose or for the placebo.

Pupil diameters were measured under bright and dim conditions before the injections (-4 hours), the next day (+20 hours), and two days later (+44 hours). Because we did not make any measurements on the weekends those subjects who were injected with Atropine on Fridays did not have their visual functions measured at 20 and 44 hours after their injection. Thus, in the data at 20 and 44 hours N is reduced from ten to six subjects. With this small N there was no statistically significant pupil diameter change for either bright or dim light conditions (see Table V). However, it should be noted that for the 1 and 2 mg doses 5 out of 6 subjects showed a larger pupil at 20 hours under bright ambient lighting. The magnitude of the dilation was rather small, ranging from 2-18% for the 1 and 2 mg doses. Only two subjects showed 15% or greater dilation at 44 hours. Under dim light conditions a few subjects had pupil diameter changes greater than 10% but these changes were in both directions (dilation & constriction) and showed no dose or subject-related patterns.

Accommodative near point was measured by "free space" and "optical" methods. We found a slight but statistically insignificant reduction in accommodation for the 2 mg dose at 20 and 44 hours after the injection. In the "free space" method the subjects had an average reduction of only 0.3 diopters with five out of six subjects showing a reduction. Using the optical method, the mean loss was 0.8 diopters and the range was from 0.1 to 3.3 diopters in the five subjects showing a reduction. In our group of young subjects, these reductions in near point are functionally

insignificant although they suggest that systemic ocular effects are long lasting and cumulative dose effects may occur with repeated usage. The optical method provides fewer cues to drive accommodation to the near limit, e.g. no convergence, and the lower values measured reflect the greater difficulty of voluntarily accommodating accurately while looking through the eyepiece of an optical system.

TABLE V

Summary of ocular function data averaged across subjects
Dose in mg/70 kg, Time in hours, +/- one SD, N=10/6/6
Pupil diameter in mm, Accommodation in diopters

Dose	Time	Pupil diameter		Accommodation	
		bright	dark	free space	optical
0	-4	5.1 +/- .8	7.3 +/- 1.3	8.4 +/- 2.2	6.5 +/- 1.7
	+20	4.9 +/- .9	7.2 +/- 1.1	8.2 +/- 2.1	6.6 +/- 1.5
	+44	4.8 +/- .7	7.2 +/- 1.1	8.2 +/- 2.2	6.6 +/- 1.7
0.25	-4	5.3 +/- .5	7.7 +/- 1.0	9.9 +/- 1.4	7.9 +/- 1.1
	+20	5.2 +/- .7	7.9 +/- .7	9.7 +/- 1.8	7.9 +/- .8
	+44	5.2 +/- .6	7.8 +/- .8	10.3 +/- 2.2	7.6 +/- 1.4
0.5	-4	5.0 +/- .7	7.2 +/- .6	9.7 +/- 1.9	7.5 +/- 1.1
	+20	5.2 +/- .5	7.1 +/- .6	9.9 +/- 2.0	8.1 +/- 2.2
	+44	5.0 +/- .4	7.1 +/- .7	10.1 +/- 1.6	8.1 +/- 2.2
1.0	-4	4.7 +/- .6	6.7 +/- 1.6	8.1 +/- 2.4	6.5 +/- 1.5
	+20	5.0 +/- .9	6.7 +/- .7	8.1 +/- 2.3	6.3 +/- 1.5
	+44	4.7 +/- .8	6.7 +/- .7	8.1 +/- 2.3	6.5 +/- 1.9
2.0	-4	4.7 +/- .7	7.3 +/- 1.3	8.8 +/- 3.2	7.1 +/- 2.1
	+20	5.0 +/- .9	7.2 +/- 1.1	8.1 +/- 2.6	6.7 +/- 2.5
	+44	5.0 +/- .8	7.4 +/- 1.3	8.5 +/- 3.2	6.3 +/- 2.1

DISCUSSION

To summarize the results of the first experiment, we found that the results of the tank tracking task indicate that atropine in doses up to 2 mg per 70 kg bodyweight does not produce a statistically significant decrement in pursuit tracking. The ocular side effects of pupil dilation and reduction in accommodative amplitude persist for the 1 and 2 mg dose for up to 44 hours after injection but are very small and functionally insignificant in the young men tested. We have also reported that the subjective symptoms of atropinization are detectable in doses as low as 0.5 mg and vary in detectability and severity among subjects at the dose levels we evaluated.

Reliability of the results of this study is demonstrated by the significant increase in tracking scores during the dim ambient light trials. This finding is consistent with earlier work with the BLASER simulator. The increased variability at the 1.0 and 2.0 mg doses may indicate a possible threshold for atropine effects beyond the 2.0 mg level. Headley's (1982) review seems to indicate that there are thresholds in some functions below which performance is not compromised, and above which it is. For example, near vision complaints are not registered for atropine doses below 3 mg, but are universal for 5 mg. The effect shown with increased tracking variability with 2 mg atropine may reflect a similar phenomenon. However, this speculation does not alter our conclusion that atropine in doses up to 2 mg does not significantly alter pursuit tracking performance.

EXPERIMENT II

The results of our first experiment provided encouraging evidence that subjects involved in a single, albeit demanding tracking task did not have their performance affected by atropine in doses up to 2 mg/70 kg body weight. The second experiment addressed the question of whether subjects in a more complex situation would have their performance degraded by atropine. In this second experiment, subjects performed a demanding tracking task while simultaneously monitoring an auditory task; they were seated in a Barany chair to produce sinusoidal motion and to perform the chair-referenced task it was necessary to suppress reflex eye movements. The subjects were able to perform these tasks and there were only small performance decrements noted at the 2 mg atropine dose.

METHODS

We selected ten male subjects for this experiment who were in good health and were not taking any medications. Our ten subjects ranged in age from 21 to 41 with a mean of 27 years. Bodyweights ranged from 54 to 94 kg with a mean of 69 kg. Our subjects had completed an average of 4.4 years of college. Seven out of ten subjects had less than one diopter of hyperopia in both eyes and were considered emmetropic and tested without any optical correction. The oldest subject (age 41) was a corrected hyperope and two subjects were corrected myopes.

Each subject spent 4-5 hours at our laboratory on each of five days of the experiment. The experiment was scheduled to be run over a 8-10 day period in order to assure that test days were at least 48 hours apart. The daily test schedule was designed with staggered injection times so that up to four subjects per day could run without creating time conflicts for use of the experimental apparatus.

The first two days were devoted to training the subjects to perform the visual and auditory tasks. We observed that repeated practice of the tasks led to large initial performance improvements and we attributed this to development of confidence and acquiring a strategy for coping with simultaneous and competing stimuli. By the end of the second training day performance levels were generally stable. Several highly self-motivated subjects continued to show small improvements in task scores throughout the experiment. Total practice time was 2.5 hours per subject.

On each test day the subjects first completed five minutes of "warm up" on the performance tasks before the first test session. Following the first test session we measured distance and near visual acuities, pulse

rate and blood pressure. After a fifteen minute waiting period the physician administered the intramuscular injection in the subject's upper arm. Each subject was tested again at 30 and 240 minutes after drug administration. Visual acuities and vital signs were checked after each session.

The experiment consisted of two performance tasks running independently and simultaneously, which the subjects were asked to perform while being rotated sinusoidally at 0.5 Hz. The first of these tasks was a pursuit tracking task in which the subject attempted to match the movements of a computer controlled target by controlling the position of a second target on the display screen. The two targets were spots subtending two minutes of arc and were generated on a Tektronics 606 scope 70 cm from the subject. At the beginning of each tracking episode the upper spot (controlled by the computer) was centered on the screen. A tracking episode consisted of the upper spot moving away from the center of the screen (randomly chosen as either left or right) at a constant velocity (also randomly selected as either .3, .6, or .9 degrees of arc per second) for 2.8 seconds . The direction was then reversed and the spot returned, at the same velocity, to the center of the screen. The upper spot then remained stationary for a period of two seconds before the next tracking episode. The subject attempted to track the upper spot using a joystick to control the lower spot. The tracking task consisted of one hundred consecutive randomly ordered tracking episodes, and lasted approximately 13 minutes.

The computer scored tracking performance by determining the absolute difference in the positions of the two dots every 91 milliseconds during each 5.6 second tracking episode. If the mean difference between dot positions during an episode was below a criterion value the subject was considered to be tracking accurately and recognition of this was indicated between episodes by briefly increasing the brightness of the upper dot. In cases where the subject did not meet the criterion for an accurate tracking response, the computer would briefly brighten the lower dot. This performance feedback was used quite successfully to motivate the subjects during the experiment.

The other performance task that occurred simultaneously and asynchronously with the visual tracking task was a tone discrimination task. The subjects listened to a sequence of high frequency (1100 Hz) and low frequency (800 Hz) tones with tones presented every 3 sec. The subject pushed a hand-held button after each low tone. The tones occurred in a preset but random sequence, with 1/5 of the tones being at the lower frequency. A half second after each low tone there was a distinctive

double tone which indicated that a low tone had just occurred and gave subjects performance feedback. If a subject pressed the button in response to a low tone, the double tone confirmed the correctness of their response. If a subject failed to respond to a low tone, the double tone reminded them to pay more attention to the tone task. The computer kept track of the number and percentage of low tones detected as well as the number and percentage of high tones correctly rejected. The subject listened to about 240 tones during the 13 minute test session.

The subject performed the visual and auditory tasks while seated in a computer controlled chair that rotated about the vertical axis. The velocity profile of the chair was sinusoidal with a frequency of 0.5 Hz and a maximum rotational velocity of 20 degrees per second. The subject's head was tilted forwards approximately 30 degrees so that the horizontal semicircular canals were maximally stimulated by the rotational accelerations. Vestibular stimulation in the absence of significant visual stimulation results in a nystagmus via the vestibular-ocular reflex (VOR). In order to perform the tracking task, subjects needed to suppress the VOR and fixate the moving spots on the screen. Eye movements were not monitored during the experiment. The chair rotation was not synchronized with the performance tasks.

RESULTS

The data gathered in this experiment were first averaged across subjects to determine means and intersubject variability. We then used the nonparametric Walsh test to determine the significance of the differences between the atropine and placebo data as was done in the first experiment.

As in our previous atropine experiments the pulse rate rose significantly following injection of atropine (see Table VI). When we applied the Walsh test to the adjusted differences, we found them to be statistically significant at 30 minutes after injection ($p<.005$) with the median increase being 26 and 44 beats per minute for 1 and 2 mg atropine doses respectively. Four hours after injection, pulse rates had returned to normal. Only one subject commented that he noticed the "racing" of his pulse. The only trend evident in the blood pressure data was a nonsignificant increase in diastolic pressure 30 minutes after injection.

TABLE VI

Summary of vital signs data averaged across subjects
Dose in mg/70 kg, Time in minutes, BP's in mm Hg, +/- one SD, N=10

Dose	Time	Pulse	Systolic BP	Diastolic BP
	-30	76 +/- 8	115 +/- 11	79 +/- 8
Placebo	+30	69 +/- 7	116 +/- 11	81 +/- 7
	+240	75 +/- 13	118 +/- 11	82 +/- 8
	-30	70 +/- 6	115 +/- 12	79 +/- 7
1.0	+30	86 +/- 10	115 +/- 12	81 +/- 7
	+240	71 +/- 9	116 +/- 8	79 +/- 8
	-30	69 +/- 8	117 +/- 6	80 +/- 9
2.0	+30	102 +/- 6	116 +/- 10	85 +/- 8
	+240	72 +/- 10	114 +/- 8	81 +/- 10

Distance acuities remained very stable throughout the experiment, averaging 20/19 across subjects. Near acuity was not affected in 9 out of 10 subjects. The oldest subject (age 41) (who had an accommodative amplitude of 4 diopters) had some difficulty reading and had a measured near acuity loss of two lines at the 40 cm test distance after the high dose of atropine. Our previous experiments indicate that young subjects given a 2 mg dose can lose 1-2 diopters of accommodation due to atropine's effect on the ciliary muscle which controls accommodation. Our visual tracking task required approximately 1.5 diopters of accommodation which is a small demand relative to the 6-10 diopter amplitude of accommodation exhibited by younger subjects.

Two measures were used to score the subject's performance in the pursuit tracking task. The first measure was a percent time-on-target score, was computed by sampling how often the subject kept his spot within a "hit" zone centered on the computer-controlled spot during each tracking episode. The "hit" zone was approximately 1 cm wide and was held constant for all target velocities and for all subjects. For each subject the median of ten trials was determined and then averaged across the ten subjects to yield time-on-target scores given in Table VII below.

TABLE VII

Median time-on-target scores (%) averaged across subjects
Dose in mg/70 kg, time in minutes, +/- one SD, N=10

Dose	Time	Slow Velocity	Medium Velocity	Fast Velocity
	-30	76.2 +/- 5.7	67.7 +/- 4.7	55.5 +/- 9.2
Placebo	+30	77.7 +/- 5.4	67.9 +/- 5.8	57.3 +/- 7.9
	+240	76.9 +/- 5.5	68.1 +/- 6.6	58.1 +/- 10.3
	-30	78.1 +/- 5.9	66.5 +/- 6.3	55.1 +/- 9.2
1.0	+30	77.9 +/- 6.6	67.3 +/- 7.1	56.2 +/- 11.1
	+240	79.9 +/- 5.7	67.8 +/- 10.0	57.2 +/- 12.3
	-30	76.5 +/- 5.5	65.8 +/- 9.8	54.9 +/- 9.0
2.0	+30	77.7 +/- 6.1	67.3 +/- 7.5	53.7 +/- 8.8
	+240	76.7 +/- 3.3	64.9 +/- 7.7	53.2 +/- 9.2

From Table VII it is clear that for the slow velocity targets the performance level remains stable across doses and test times. For the fast velocity targets which are definitely more difficult to track there appears to be a decrease in performance level for the 2 mg dose, while there is an improvement in successive session scores for the placebo and 1 mg doses. When the Walsh test was applied to the adjusted intersession score differences, the only statistically significant difference occurred with the 2 mg dose at 240 minutes after injection when the median difference averaged across subjects was -2% ($p<.056$).

The second measure of tracking performance that we used was the mean of the sampled tracking errors measured during each tracking episode. This measure was independent of the direction of error, so it did not matter if the subject was leading or lagging the target. This measure was also independent of performance feedback criteria. A score of zero would indicate that the stimulus had been tracked perfectly. The unit of measurement was roughly equivalent to 0.5 minutes of arc. The median of each subject's scores were averaged across subjects and the data are shown in Table VIII below.

TABLE VIII

Summary of median tracking error scores averaged across subjects
Dose in mg/70 kg, Time in minutes, Scores in display units, +/- one SD, N=10

Dose	Time	Slow Velocity	Medium Velocity	Fast Velocity
	-30	13.6 +/- 1.7	17.4 +/- 1.9	23.1 +/- 3.8
Placebo	+30	13.0 +/- 1.8	17.2 +/- 1.7	21.6 +/- 2.7
	+240	13.2 +/- 2.0	17.0 +/- 2.1	21.9 +/- 4.1
	-30	13.2 +/- 1.9	17.9 +/- 2.3	22.5 +/- 3.9
1.0	+30	12.9 +/- 1.8	17.3 +/- 2.6	22.3 +/- 4.8
	+240	12.6 +/- 1.8	17.5 +/- 3.6	22.0 +/- 4.9
	-30	13.4 +/- 1.8	17.9 +/- 3.4	23.0 +/- 3.8
2.0	+30	13.1 +/- 2.2	17.0 +/- 2.3	23.4 +/- 3.7
	+240	13.2 +/- 1.9	18.4 +/- 2.4	23.6 +/- 4.0

The averaged data in the table above show that with the placebo there is a trend of improving scores during each session of the test day. This trend is a sign of a continuation of the learning process but is very small compared to the improvement seen during the training sessions. Randomization of the administration of the doses balances out the accumulated practice effect on the averaged test scores.

The slow and medium velocity tracking data show no drug effect and this is confirmed by applying the Walsh test to the adjusted difference data. None of the differences proved significant. The drug effect does appear when testing the significance of the adjusted difference scores for the fast velocity targets. Here the Walsh test shows that the 1 mg dose produces a significant decrement in the third test session ($p<.056$) and the 2 mg dose produces decrements at both 30 and 240 minutes after injection ($p<.056$). It appears that the subject is unable to improve his scores under the influence of atropine and frequently the scores worsen. This may be due to either fatigue or to other effects of atropine which hamper performance during stressful conditions. Performance decrements are only elicited when the subject is under significant stress, in this case, when attempting to track the more difficult targets movement.

DISCUSSION

The results of these and our previous experiments confirm the known physiological effects of atropine on general cardiovascular and autonomic funtion. The results of our tracking experiments provide evidence that atropine in doses up to 2 mg will not greatly interfere with performance of demanding tasks involving precise tracking at different luminance levels or with simultaneous auditory monitoring while the subject is in motion.

There is some indication, however, that we are at a threshold point for deterioration of performance; in the most demanding tracking task of the BLASER simulator, there is increased variance of response at the 2 mg atropine dose. In the most demanding tracking condition in the SKIVS experiment there is deterioration of performance relative to placebo. The literature reviewed by Headley (1982) indicates that for near vision tasks, there is a threshold for deterioration of near vision even in young subjects, between 3 and 5 mg of atropine. It is likely that a similar threshold exists for the tracking tasks such as those we have used.

Prolonged effects of atropine are the rule rather than the exception in the ophthalmological usage of atropine, and so we are not greatly surprised to be able to measure ocular effects of the drug for up to 44 hours after administration. These effects would be greater for larger doses of the drug, and in susceptible personnel may produced a prolonged reduction in function and operational efficiency.

The oldest of our subjects in the SKIVS tracking experiment, a pre-presbyope aged 41, showed a significant deterioration of near vision after administration of 2 mg of atropine. This effect could be a source of significant visual disability for command personnel in this age range, as we had predicted in our earlier reports. We feel that it should be investigated further.

Fatigue effects interacting with atropine effects appear to have been influencing tracking performance in the SKIVS experiment. This may be a potential problem in continuous operations. Experiments to examine these effects for higher doses of atropine and for atropine in combination with pre-treatment compounds such as pyridostigmine and other drugs used for treatment of organophosphate poisoning should be conducted.

In summary, we find small effects on tracking performance in our experiments, confirm the well known more general physiological effects and suspect that we are at a dose-threshold for major atropine effects on field-related performance tasks.

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APPENDIX

ATROPINE SYMPTOM CHECKLIST

Subject Initials: _____ Date : / /82

Numbers refer to these phrases: 0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

Please circle the appropriate point on the scale for each of the following feelings or symptoms. Describe how you are feeling now.

	None				Extreme	Observer's Comments
Dry mouth	0	1	2	3	4	
Dry skin	0	1	2	3	4	
Blurred distance vision	0	1	2	3	4	
Blurred near vision	0	1	2	3	4	
"High" or intoxicated	0	1	2	3	4	
Feeling hot	0	1	2	3	4	
Disturbed sense of balance	0	1	2	3	4	
Impaired coordination	0	1	2	3	4	
Tense	0	1	2	3	4	
Restless	0	1	2	3	4	
Depressed	0	1	2	3	4	
Anxious	0	1	2	3	4	
Fatigued	0	1	2	3	4	
Unable to concentrate	0	1	2	3	4	
Confused	0	1	2	3	4	
Forgetful	0	1	2	3	4	
Muddled	0	1	2	3	4	
Bewildered	0	1	2	3	4	
Uncertain about things	0	1	2	3	4	

Pulse _____ Blood pressure ___/___

Physician's Initials _____ Time ___:___

PERSONNEL

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